REVISTA BRASILEIRA DE REUMATOLOGIA
www.reumatologia.com.br
SOCIEDADE BRASILEIRA DE REUMATOLOGIA

Original article

Anti-synthetase syndrome: anti-PL-7, anti-PL-12 and anti-EJ

Fernando Henrique Carlos de Souza[a], *Marcela Gran Pina Cruellas*[b], *Mauricio Levy-Neto*[a], *Samuel Katsuyuki Shinjo*[a]

[a]*Rheumatology Service, Clinical Hospital, School of Medicine, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil*
[b]*Rheumatology Division, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil*

ARTICLE INFO

Article history:
Received 20 July 2012
Accepted 19 February 2013

Keywords:
Aminoacyl-tRNA synthetases
Inflammatory myopathy
Myositis
Antisynthetase syndrome

ABSTRACT

Objectives: Due to the scarcity of studies in the literature, we conducted an analysis of a series of patients with the anti-PL-7, PL-12 and EJ types of antisynthetase syndrome (ASS).
Methods: We conducted a retrospective cohort study of 20 patients with ASS (8 with anti-PL-7, 6 with PL-12, 6 with EJ) monitored in our department between 1982 and 2012.
Results: The mean patient age at disease onset was 38.5 ± 12.9 years, and the disease duration was 4.5 ± 6.4 years. Of all the patients, 70% were white and 85% were female. Constitutional symptoms occurred in 90% of cases. All patients presented objective muscle weakness in the limbs; in addition, 30% were bedridden and 65% demonstrated high dysphagia at diagnosis. Joint and pulmonary involvement and Raynaud's phenomenon occurred in 50%, 40% and 65% of cases, respectively, with more than half of the patients presenting incipient pneumopathy, ground-glass opacity and/or pulmonary fibrosis. There were no cases of neurological and/or cardiac involvement. All patients received prednisone or other immunosuppressants depending on tolerance, side effects and/or disease refractoriness. Importantly, patients with the anti-EJ type of ASS demonstrated higher rates of recurrence. Two patients died during follow-up, and 1 patient had breast cancer at the time of diagnosis.
Conclusions: ASS (anti-PL-7, PL-12 and EJ) was found to predominantly affect white women. Although the autoantibodies described in the present study are more related to pulmonary than joint involvement, our patients showed a significant percentage of both types of involvement and a high percentage of myopathy. We also observed a low mortality rate.

Síndrome antissintetase: anti-PL-7, anti-PL-12 e anti-EJ

Palavras-chave:
Aminoacil-tRNA sintetases
Miopatia inflamatória
Miosite
Síndrome antissintetase

RESUMO

Objetivos: Devido à escassez de trabalhos na literatura, realizamos análise de uma série de pacientes com síndrome antissintetase (SAS) do tipo anti-PL-7, PL-12 e EJ.
Métodos: Estudo de coorte, retrospectivo, envolvendo 20 pacientes com SAS (8 com anti-PL-7, 6 com PL-12, 6 com EJ), em acompanhamento em nosso serviço, entre 1982 e 2012.
Resultados: A média de idade dos pacientes ao início da doença foi de 38,5 ± 12,9 anos, e a duração da doença de 4,5 ± 6,4 anos. Setenta por cento dos pacientes eram brancos e 85% eram mulheres. Sintomas constitucionais ocorreram em 90% dos casos. Todos apresentavam fraqueza muscular objetiva dos membros; ao diagnóstico, 30% encontravam-

* *Corresponding author.*
E-mail: samuel.shinjo@gmail.com (S.K. Shinjo).
0482-5004/$ - see front matter.

-se acamados e 65% com disfagia alta. Envolvimento articular, pulmonar e fenômeno de Raynaud ocorreram, respectivamente, em 50%, 40% e 65% dos casos; mais da metade dos pacientes apresentava pneumopatia incipiente, opacidade em vidro-fosco e/ou fibrose pulmonar. Não houve casos de envolvimento neurológico e/ou cardíaco. Todos receberam prednisona e, como poupadores dessa medicação, diferentes imunossupressores, dependendo da tolerância, efeitos colaterais e/ou refratariedade da doença. De relevância, os pacientes com anti-EJ apresentaram maiores taxas de recidiva. Dois pacientes evoluíram para óbito ao longo do seguimento, e um paciente teve neoplasia mamária na ocasião do diagnóstico da doença.

Conclusões: A SAS (anti-PL-7, PL-12 e EJ) afetou predominantemente mulheres brancas. Embora os autoanticorpos descritos no presente estudo estejam mais relacionados com o acometimento pulmonar comparativamente ao articular, nossos pacientes apresentaram uma porcentagem significativa de ambos e com percentagem alta de miopatia. Além disso, houve menor taxa de mortalidade.

Introduction

Antisynthetase syndrome (ASS) is an idiopathic inflammatory myopathy characterised by the presence of anti-aminoacyl tRNA synthetase antibodies, such as anti-Jo-1 (histidyl-), anti-PL-7 (threonyl-), anti-PL-12 (alanyl-), anti-EJ (glycyl-) and anti-OJ (isoleucyl-) antibodies.[1-3] The most frequently reported autoantibodies are those targeting Jo-1.[1-3]

Clinically, ASS is characterised by muscular (myositis), pulmonary (interstitial lung disease) and joint (arthritis) involvement; fever; Raynaud's phenomenon and mechanic's hands.[1-3] As a rare syndrome, the prevalence of ASS in the general population is unknown. Moreover, there are few epidemiological studies on ASS, and those that do exist are mainly based on anti-Jo-1 ASS,[3-7] while research on ASS targeting other aminoacyl-tRNA synthetases is limited to a few case reports.[8-11]

The present study therefore presents a series of patients with the anti-PL-7, anti-PL-12 and anti-EJ types of ASS.

Patients and methods

Of the 222 patients monitored at our tertiary centre between 1980 and 2012 with a confirmed diagnosis of idiopathic inflammatory myopathy, 20 patients with anti-PL-7, anti-PL-12 or anti-EJ ASS were identified and analysed. All 20 patients met the Bohan and Peter criteria[12] and presented with fever at the time of disease onset, as well as Raynaud's phenomenon, mechanic's hands and muscular, pulmonary and/or joint involvement. This study was approved by the local ethics committee (HC Research Protocol No. 0039/10).

Demographic, therapeutic, clinical and laboratory data were obtained following a systematic review of patient charts. The following parameters were analysed as clinical manifestations: constitutional symptoms; skin changes (heliotrope, Gottron's papules, Raynaud's phenomenon); joint involvement (arthralgia and/or arthritis); the presence of dysphagia, dysphonia and dyspnoea; the proximal muscle strength of the limbs (grade 0: absence of muscle contraction; grade I: signs of slight contractility; grade II: normal range of motion, but not against gravity; grade III: normal range of motion against gravity; grade IV: full mobility against gravity and degree of resistance; grade V: complete mobility against strong resistance and against gravity) and neurological or cardiac involvement.

The laboratory analyses took place at the onset of diagnosis and prior to the introduction of corticosteroids. Data for the levels of creatine kinase (reference value: 24-173 U/L) and aldolase (1.0-7.5 U/L) were obtained using the automated kinetic method.

For autoantibody analysis, we used sera samples stored in a freezer (–20 °C) that had been routinely collected at the time of ASS diagnosis. Autoantibodies were evaluated using a solid-phase commercial kit with immunoblotting; this qualitative immunoassay could detect 11 human immunoglobulin G (IgG) autoantibodies against myositis-specific antigens among those present in the serum or plasma (Euroimmun, Lübeck, Germany). To increase the specificity of the method, the manufacturer's protocol was applied. The degree of positivity of the reaction was arbitrarily defined as negative, weak (+/+++), moderate (++/+++) or strong (+++/+++) by two independent researchers (MGPC and SKS), and both positive and negative controls were included as a reference. In the present study, we considered only cases with moderate to intense positivity for the analysis.

Complementary examinations (thorax radiography, computed tomography, electrocardiography, electroneuromyography and muscle biopsy from the brachial biceps or anterolateral thigh muscle) were performed as a routine procedure for the initial medical consultations related to an ASS diagnosis.

Disease recidivism was defined as recurrence of clinical manifestations and/or increased muscle enzyme serum levels attributed to disease activity or progression of pulmonary injury (clinical or radiological), following the exclusion of possible infectious or neoplastic processes.

Corticosteroid therapy was initially used (prednisone 1 mg/kg/day, orally), followed by a gradual dose reduction according to the clinical and laboratory results. In cases of severe disease (progression of dyspnoea, dysphagia, significant loss of muscular strength), pulse therapy was performed with methylprednisolone (1 g/day for three consecutive days) and/

or human intravenous immunoglobulin (1 g/kg/day for two consecutive days).

The following immunosuppressants were used to spare corticosteroids: azathioprine (2-3 mg/kg/day), methotrexate (20-25 mg/week), cyclosporin (2-4 mg/kg/day), mycophenolate mofetil (2-3 g/day), leflunomide (20 mg/day), monthly intravenous cyclophosphamide (0.5-1.0 g/m^2 body surface) and chloroquine diphosphate (3-4 mg/kg/day).

The results are expressed as the means ± standard deviation (SD), medians [interquartile] or percentages (%).

Results

Twenty consecutive patients with ASS were analysed over 32 years. Among the autoantibody types of ASS analysed, eight patients had anti-PL-7, six had anti-PL-12, and six had anti-EJ autoantibodies. In the total population analysed, there were no cases of anti-OJ ASS, which is why this types was not addressed in this study. All patients were also positive for antinuclear antibodies (ANA - Hep2) with titres ≥ 1/200 [homogeneous nuclear pattern in 6 (30%) cases and cytoplasmic in 15 (75%) cases]. Table 1 shows the demographic, clinical and laboratory characteristics of these patients.

ASS predominantly affected white individuals (70%) and females (85%), with a mean age at disease onset of 38.5 ± 12.9 years (range: 17-63 years) and a mean disease duration of 4.5 ± 6.4 years (range: 1-30 years). In our sample, all patients in the anti PL-7 and anti-EJ groups were female.

Constitutional symptoms were observed in 90% of cases and in 100% of patients with anti-PL-7 ASS. Joint and skin involvement and Raynaud's phenomenon occurred in approximately half of the patients. All patients demonstrated objective muscle weakness in the limbs (upper and/or lower), with the majority of cases scored as grade III or IV and no cases of grade I or II. Regarding prognostic factors of the disease, 30% of patients were bedridden, and two-thirds had high dysphagia at diagnosis. Involvement of the upper respiratory tract occurred in 15% of cases, whereas dyspnoea (moderate to great effort) was present in half of the cases, equally distributed across all groups. There were no cases of neurological and/or cardiac involvement (coronary syndrome, deep vein thrombosis or stroke).

The levels of serum creatine kinase and aldolase at disease onset were 1,124 [812-8,500] U/L and 28.4 [15.7-55.9] U/L, respectively. The highest values were obtained in the anti-EJ subgroup.

In relation to pulmonary imaging (computed tomography) findings, nearly half of the patients demonstrated evidence of incipient pneumopathy, ground-glass lesions and/or basal pulmonary fibrosis. The anti-PL-7 patients also demonstrated greater pulmonary involvement, with a predominance of ground-glass lesions.

Regarding initial treatment, all patients received corticosteroids (prednisone 1 mg/kg/day), and seven patients (35.0%) received additional methylprednisolone pulse therapy; there was a greater need for this additional therapy in the anti-EJ subgroup (Table 2).

Various immunosuppressive agents were used, depending on tolerance, side effects and refractoriness, and these included azathioprine (55.0%), methotrexate (25.0%), cyclosporine (5.0%) and human intravenous immunoglobulin (5.0%). Parenteral cyclophosphamide (25.0%) was administered as monotherapy or in combination with other immunosuppressants to treat pulmonary disease.

Disease recidivism (clinical and/or laboratory) occurred in approximately one-third of cases, principally in the anti-EJ group.

Neoplasia (mammary) occurred in one patient (5.0%) in the anti-EJ group at the time of a diagnosis of inflammatory myopathy. This patient underwent radical mastectomy with the resolution of neoplasia.

Table 1 – Demographic, clinical and laboratory characteristics of the 20 patients with anti-PL-7, anti-PL-12 or anti-EJ antisynthetase syndrome.

	Total (n = 20)	Anti-PL-7 (n = 8)	Anti-PL-12 (n = 6)	Anti-EJ (n = 6)
Female	17 (85.0)	8 (100.0)	3 (50.0)	6 (100.0)
White	14 (70.0)	6 (75.0)	3 (50.0)	5 (83.3)
Mean age at diagnosis	38.5 ± 12.9	38.4 ± 10.0	40.3 ± 17.3	36.7 ± 13.5
Mean duration of disease	4.5 ± 6.4	1.5 ± 0.5	3.5 ± 2.1	9.0 ± 10.7
Constitutional symptoms	18 (90.0)	8 (100.0)	5 (83.3)	5 (83.3)
Skin involvement				
Heliotrope	10 (50.0)	3 (37.5)	3 (50.0)	4 (66.7)
Gottron's papules	8 (40.0)	3 (37.5)	1 (16.7)	4 (66.7)
Raynaud's phenomenon	8 (40.0%)	4 (50.0)	2 (33.3)	2 (33.3)
Muscular involvement				
Upper limbs				
Grade V	3 (15)	1 (12.5)	2 (33.3)	1 (16.7)
Grade IV	12 (60.0)	4 (50.0)	4 (66.7)	4 (66.7)
Grade III	5 (35.0)	3 (37.5)	0	1 (16.7)
Grade II or I	0	0	0	0
Lower limbs				
Grade V	0	0	0	0
Grade IV	14 (70.0)	5 (63.5)	4 (66.7)	5 (83.3)
Grade III	6 (30.0)	3 (37.5)	2 (33.3)	1 (16.7)
Grade II or I	0	0	0	0
Bedridden	6 (30.0)	4 (50.0)	1 (16.7)	1 (16.7)
Joint involvement	10 (50.0)	4 (50.0)	3 (50.0)	5 (83.3)
GIT involvement				
Dysphagia	13 (65.0)	6 (75.0)	2 (33.3)	2 (33.3)
RT involvement	13 (65.0)	5(63.5)	4 (66.7)	4 (66.7)
Dysphonia	3 (15.0)	1 (12.5)	1 (16.7)	1 (16.7)
Dyspnoea	10 (50.0)	4 (50.0)	3 (50.0)	3 (50.0)
Neurological involvement	0	0	0	0
Cardiac involvement	0	0	0	0
Creatine kinase (U/L)	1124 [812-8500]	3350 [1079-5400]	812 [45-1040]	2787 [1000-3500]
Aldolase (U/L)	28.4 [15.7-55.9]	34.5 [20.8-73.9]	15.7 [4-39]	87.4 [15.7-159.0]
CT Thorax				
Ground-glass (%)	9 (45.0)	4 (50.0)	2 (33.3)	3 (50.0)
Nodules (%)	2 (10.0)	1 (16.7)	1 (10.0)	0
Bibasilar fibrosis (%)	3 (15.0)	2 (25.0)	0	1 (16.7)

IVIG, human intravenous immunoglobulin; CT, computerised tomography; GIT, gastrointestinal tract; RT, respiratory tract.
Results are expressed as means (standard deviation), medians [interquartile] or percentages (%).

Table 2 – Medicinal treatment and evolution of the 20 patients with anti-PL-7, anti-PL-12 or anti-EJ antisynthetase syndrome.

	Total (n = 20)	Anti-PL-7 (n = 8)	Anti-PL-12 (n = 6)	Anti-EJ (n = 6)
Methylprednisolone	7 (35.0)	1 (12.5)	2 (33.3)	4 (66.7)
Prednisone	20 (100.0)	8 (100.0)	6 (100.0)	6 (100.0)
Azathioprine	11 (55.0)	4 (50.0)	2 (33.3)	5 (83.3)
Methotrexate	5 (25.0)	1 (12.5)	4 (66.7)	0
Cyclosporine	1 (5.0)	0	1 (16.7)	0
Cyclophosphamide	5 (25.0)	1 (12.5)	2 (33.3)	2 (33.3)
IVIG	1 (5.0)	1 (12.5)	0	0
Recidivism	6 (30.0)	2 (25.0)	1 (16.7)	3 (50.0)
Neoplasia	1 (5.0%)	0	0	1 (16.7)
Deaths	2 (10.0)	1 (12.5)	1 (16.7)	0

IVIG, human intravenous immunoglobulin.
Results are expressed as means (standard deviation), medians [interquartile] or percentages (%).

During follow-up, 2 patients died. One patient in the anti-PL-12 group died due to gluteal abscess and sepsis, and 1 patient in the anti-PL-7 group died due to aspiration pneumonia associated with high dysphagia.

Discussion

This report presents the clinical, laboratory and evolutionary characteristics of a series of 20 patients with anti-PL-7, anti-PL-12 and anti-EJ ASS. As epidemiological studies in the literature are rare,[8-11,13] this study provides an overview of these subgroups of patients.

ASS primarily affects adults and demonstrates a male-to-female ratio of 1:2.3.[1-14] In the present study, ASS affected only females, with the exception of the anti-PL-12 group, in which the disease affected both genders equally.

ASS generates antibodies against various aminoacyl-tRNA synthetases, which are cytoplasmic proteins that catalyse the coupling of specific amino acids to tRNA.[2-15] The presence of these antibodies is found in approximately 20-40% of adults with polymyositis and 5% of adults with dermatomyositis,[1-3,13] with anti-Jo-1 being the most common type of autoantibody.[16-18] We recently presented the clinical and laboratory profiles of patients with anti-Jo-1 ASS.[7] In the present study, we evaluated only patients with anti-PL-7, anti-PL-12 or anti-EJ ASS. The identification of autoantibodies against aminoacyl-tRNA synthetases is essential for the diagnosis of ASS, although to date, there are no standardised and validated laboratory tests for the characterisation of these autoantibodies.[13] Despite this limitation, we used a commercial kit for the detection of these autoantibodies.

The clinical manifestations of ASS typically translate into myositis, interstitial lung disease and/or joint involvement. The presence of fever, Raynaud's phenomenon and mechanic's hands is also observed.[17,18]

Muscular involvement is found in more than 90% of ASS cases, with manifestations such as myalgia, muscle weakness, atrophy and fibrosis. The initial manifestation generally involves proximal muscle weakness of the limbs.[1] These changes can be detected in muscle biopsies or using electromyography and often result in increased levels of muscle enzymes. Our patients showed a significant increase in muscle enzyme serum levels early in disease development as well as objective muscle weakness of the upper and/or lower limbs. Patients with anti-PL-7 ASS presented higher overall weakness in our study despite serum muscle enzyme values higher that those observed in the anti-EJ subgroup of patients. Therefore, in this population, a linear relationship between laboratory abnormalities and greater severity of muscular is not necessarily present at diagnosis.

Pulmonary involvement, even in the absence of muscular changes, is observed in more than 60% of cases and is the leading cause of morbidity.[19,20] In some cases, interstitial lung disease is prevalent in ASS; this condition has a rapid onset, leading to acute respiratory failure and occasionally causing patients to be highly refractory to established treatments.[21,22] The pulmonary manifestations described include dyspnoea, cough, thoracic pain, exercise intolerance and respiratory failure.[21] Antisynthetase antibodies, particularly anti-PL-7 and anti-PL-12 antibodies, are strongly associated with interstitial pulmonary disease, and this association appears in 90-100% of cases.[10,19,22,23] In a previous analysis of large numbers of idiopathic interstitial pneumonias, the occurrence of ASS was not rare, with most cases linked to the anti-EJ subtype.[23] In our sample, dyspnoea and pulmonary abnormalities occurred at similar rates in the 3 subgroups studied and less frequently than previously described in the literature.[10,19,23]

Radiological images may reveal an interstitial pattern of ground-glass lesions, linear opacities, parenchymal consolidations and/or micronodules with evidence of restrictive lung function.[20,24] In the present study, almost one-half of the patients demonstrated evidence of incipient pneumopathy, ground-glass lesions and/or basal pulmonary fibrosis using computed tomography at high resolution.

Joint involvement, such as arthralgia and/or arthritis with or without bone erosion, affects 50% of ASS cases,[25] and data from the present study support this prevalence. Raynaud's phenomenon, mechanic's hands, photosensitivity, malar rash and cutaneous vasculitis may also be observed in ASS patients.[25] Cardiac involvement has also been reported, but its prevalence appears not to differ from that of dermatomyositis/polymyositis.[26] In the present study, one-half of the patients (mostly anti-EJ cases) presented skin changes, but there were no cases of cardiac involvement.

Corticosteroid therapy is the first-line treatment for myositis as well as interstitial pneumopathy in ASS.[27] In the present study, all patients received corticosteroids. In addition, one-third of the patients required pulse therapy with methylprednisolone due to the severity of the disease (high dysphagia, being bedridden and/or progression of objective dyspnoea).

No consensus has been reached regarding the use of immunosuppressants in ASS patients, as the available evidence in the literature is weak and based on case reports and reviews.[28-30] In addition to this lack of consensus, the management of immunosuppressants may vary according to regional experience and the specialisation by which the patients have been monitored, such as neurology, pulmonology and/or rheumatology. In the present study, as our experience was set in the context of a rheumatology service, the immunosup-

pressants most routinely used in patients with ASS included azathioprine, cyclophosphamide and methotrexate.

Following the administration of corticosteroids, all patients experienced initial remission of the disease, in contrast to reports in the literature describing a remission rate of 21-68%.[31,32] This discrepancy may be explained by the more frequent use of pulse therapy in the current study. Disease recidivism occurred in one-third of our patients, mostly in patients with the anti-PL-7 subtype, whereas data from the literature indicate that recidivism occurs in approximately 6-43% of cases.[26,31]

The mortality rate in patients with ASS varies between 12 and 40%.[33-35] However, only 2 of our patients died (one due to gluteal abscess and sepsis, and the other due to aspiration pneumonia secondary to high dysphagia), which indicates that our study had a low mortality rate.

In addition, we reported 1 case of neoplasia (breast) that was identified at the time of diagnosis with anti-EJ ASS. On this occasion, radical mastectomy was performed, with resolution of the neoplasm.

One limitation of the present study was that we analysed only patients with ASS who were monitored at a tertiary service, which may not reflect the actual distribution of patients with ASS in our environment. Furthermore, patients who were monitored in other specialties such as pulmonology (where patients forming part of the ASS group with defined interstitial lung disease may be monitored independently of muscular involvement) were not included.

In conclusion, anti-PL-7, anti-PL-12 and anti-EJ ASS affected predominantly white women in our study population. Although the autoantibodies described in the present study are more related to pulmonary than joint involvement, our patients showed a significant percentage of both types of involvement, with a higher percentage of muscular involvement. We also observed a low mortality rate among ASS patients. However, studies with larger sample sizes are needed to verify the accuracy of these associations.

Financial support

S.K. Shinjo (Federico Foundation) and M.A.P. Cruellas (São Paulo Research Foundation - FAPESP # 2012/03399-9). The present study was supported by the São Paulo Research Foundation - FAPESP #2011/12700-1.

Conflicts of Interest

The authors declare no conflicts of interest.

REFERENCES

1. Medsger TA, Oddis CV. Inflammatory muscle disease. Clinical features. In: Rheumatology. Eds JH Klippel, PA Dieppe. London, UK: Mosby; 1994.
2. Hengstman GJ, van Engelen BG, van Venrooij WJ. Myositis specific autoantibodies: changing insights in pathophysiology and clinical associations. Curr Opin Rheumatol. 2004;16(6):692-9.
3. Imbert-Masseau A, Hamidou M, Agard C, Grolleau JY, Chérin P. Antisynthetase syndrome. Joint Bone Spine. 2003;70(3):161-8.
4. Späth M, Schröder M, Schlotter-Weigel B, Walter MC, Hautmann H, Leinsinger G, et al. The long-term outcome of anti-Jo-1-positive inflammatory myopathies. J Neurol. 2004;251(7):859-4.
5. Gran JT. Anti-synthetase syndrome. Tidsskr Nor Laegeforen. 2009;129(16):1631.
6. Váncsa A, Csípo I, Németh J, Dévényi K, Gergely L, Dankó K. Characteristics of interstitial lung disease in SS-A positive/Jo-1 positive inflammatory myopathy patients. Rheumatol. Int 2009;29(9):989-94.
7. Shinjo SK, Levy-Neto M. Anti-Jo-1 antisynthetase syndrome. Rev Bras Reumatol. 2010;50(5):492-500.
8. Kalluri M, Sahn SA, Oddis CV, Gharib SL, Christopher-Stine L, Danoff SK, et al. Clinical profile of anti-PL-12 autoantibody. Cohort study and review of the literature. Chest. 2009;135(6):1550-6.
9. Targoff IN, Arnett FC. Clinical manifestations in patients with antibody to PL-12 antigen (alanyl-tRNA synthetase). Am J Med. 1990;88(3):241-51.
10. Labirua A, Lundberg IE. Interstitial lung disease and idiopathic inflammatory myopathies: progress and pitfalls. Curr Opin Rheumatol. 2010;22(6):633-8.
11. Labirua-Iturburu A, Selva-O'Callaghan A, Vincze M, Dankó K, Vencovsky J, Fisher B, et al. Anti-PL-7 (anti-threonyl-tRNA synthetase) antisynthetase syndrome: clinical manifestations in a series of patients from a European multicenter study (EUMYONET) and review of the literature. Medicine (Baltimore) 2012. [In press].
12. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292(7):344-7.
13. Ghirardello A, Rampudda M, Ekholm L, Bassi N, Tarricone E, et al. Diagnostic performance and validation of autoantibody testing in myositis by a commercial line blot assay. Rheumatology (Oxford). 2010;49(12):2370-4.
14. Hengstman GJD, van Venrooij WJ, Vencovsky J, Moutsopoulos HM, van Engelen BGM. The relative prevalence of dermatomyositis and polymyositis in Europe exhibits a latitudinal gradient. Ann Rheum Dis. 2000;59(2):141-2.
15. Plotz PH, Targoff I. Myositis associated antigens. Aminoacyl-tRNA synthetases. In: Manual of Biological Markers of Disease. Eds, WJ Van Venrooij, R Maini. The Netherlands: Kluwer Academic Publications. 1994;1(6):1-18.
16. Nishikai M, Reichlin M. Heterogeneity of precipitating antibodies in polymyositis and dermatomyositis. Characterization of the Jo-1 antibody system. Arthritis Rheum. 1980;23(8):881-8.
17. Brouwer R, Hengstman GJD, Vree Egberts W, Ehrfeld H, Bozic B, Ghirardello A, et al. Autoantibody profiles in the sera of European patients with myositis. Ann Rheum Dis. 2001;60(2):116-23.
18. Love LA, Leff RL, Fraser DD, Targoff IN, Dalakas M, Plotz PH, et al. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. Medicine. (Baltimore) 1991;70(6):360-74.
19. Gugliemi S, Merz M, Gugger M, Suter C, Nicod LP. Acute respiratory distress syndrome secondary to antisynthetase syndrome is reversible with tacrolimus. Eur Respir J. 2008;31(1):213-7.
20. Clawson K, Oddis CV. Adult respiratory distress syndrome in polymyositis patients with the anti-Jo-1 antibody. Arthritis Rheum. 1995;38(10):1519-23.
21. Marie I, Hatron PY, Hachulla E, Wallaert B, Michon-Pasturel U, Devulder B. Pulmonary involvement in polymyositis and in dermatomyositis. J Rheumatol. 1998;25(7):1336-13.

22. Ikezoe J, Johkoh T, Kohno N, Takeuchi N, Ichikado K, Nakamura H. High-resolution CT findings of lung disease in patients with polymyositis and dermatomyositis. J Thorac Imaging. 1999;11(4):250-9.
23. Watanabe K, Handa T, Tanizawa K, Hosono Y, Taguchi Y, et al. Detection of antisynthetase syndrome in patients with idiopathic interstitial pneumonias. Respir Med. 2011;105(8):1238-47.
24. Akira M, Hara H, Sakatani M. Interstitial lung disease in association with polymyositis-dermatomyositis: long-term follow-up CT evaluation in seven patients. Radiology. 1999;210(2):333-8.
25. Targoff IN, Arnett FC. Clinical manifestations in patients with antibody to PL-12 antigen (alanyl-tRNA synthetase). Am J Med. 1990;88(3):241-51.
26. Poveda Gomez F, Merino JL, Mate I, Sobrino JA, Camacho J, Gamallo C. Polymyositis associated with anti-Jo1 antibodies: severe cardiac involvement as initial manifestation. Am J Med. 1993;94(1):110-1.
27. Handa T, Nagai S, Kawabata D, Nagao T, Takemura M, Kitaichi M et al. Long-term clinical course of a patient with anti PL-12 antibody accompanied by interstitial pneumonia and severe pulmonary hypertension. Intern Med. 2005;44(4):319-25.
28. Douglas WW, Tazelaar HD, Hartman TE, Hartman RP, Decker PA, Schroeder DR, et al. Polymyositis-dermatomyositis-associated interstitial lung disease. Am J Respir Crit Care Med. 2001;164(7):1182-5.
29. Wilkes MR, Sereika SM, Fertig N, Lucas MR, Oddis CV. Treatment of antisynthetase-associated interstitial lung disease with tacrolimus. Arthritis Rheum. 2005;52(8):2439-46.
30. Kenji N, Masayoshi H, Masako H, Yasuyuki Y, Takao K, Nobuyuki M. Efficacy of cyclosporine treatment to interstitial pneumonitis associated with polymyositis and dermatomyositis. Arthritis Rheum. 2001;44:S353.
31. Frost NA, Morand EF, Hall CL, Maddison PJ, Bhalla AK. Idiopathic polymyositis complicated by arthritis and mesangial proliferative glomerulonephritis: case report and review of the literature. Br J Rheumatol. 1993;32(10):929-31.
32. Selva-O'Callaghan A, Labrador-Horrilllo M, Solans-Laque R, Pilar Simeon-Aznar C, Martinez-Gomez X, Viardell-Tarres M. Myositis specific and myositis-associated antibodies in a series of eighty-eight Mediterranean patients with idiopathic inflammatory myopathy. Arthritis Rheum. 2006;55(5):791-8.
33. Lee W, Zimmermann B 3rd, Lally EV. Relapse of polymyositis after prolonged remission. J Rheumatol. 1997;24(8):1641-4.
34. Tillie-Leblond I, Wislez M, Valeyre D, Crestani B, Rabbat A, Israel-Biet D, et al. Interstitial lung disease and anti-Jo-1 antibodies: difference between acute and gradual onset. Thorax. 2008;63(1):53-9.
35. Bronner IM, van der Meulen MFG, de Visser M, Kalmijn S, van Venrooij WJ, Voskuyl AE, et al. Long-term outcome in polymyositis and dermatomyositis. Ann Rheum Dis. 2006;65(11):1465-61.